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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,788	MAHAN ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,7,13 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,7,13,20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 2,4,7,13 and 20 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. All claims have been amended to recite the term "immunoprotective".

Allowable subject matter Withdrawn

1. Claim 20 which was previously indicated as being allowable over the prior art of record, is no longer allowable in light of a New Grounds of Rejection necessitated by Applicant's amendment requiring all antigens expressed by the attenuated form of live bacteria to be immunoprotective antigens, and claim 20 is directed to HIV antigen. No protective HIV antigens are known in the art to prevent or treat HIV/AIDS, thus necessitating new grounds of rejection under 35 USC 112, first paragraph enablement.

Rejections Withdrawn

2. Claims 13 and 7 rejected under 35 USC 102(e) as anticipated by Kleanthous et al (US Pat. 6,585,975, as evidenced by Torreblanca et al(1996) is herein withdrawn in light of the fact that Kleanthous et al disclose attenuated Salmonella strains (see page 18, last paragraph) with aroA, phoP, pagC, cya and crp mutations all of which could alter Dam activity, but no specific dam gene mutations.

Objections/Rejections Maintained

1. Claims 2,4 and 7 objected to because of the following informalities: Claims 2, 4 and 7 depend from a later presented claim and should depend from a prior claim, is maintained for reasons of record until such time that the claim renumbering has been affected.

2. Claims 13, 2, 4 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Torreblanca et al(1996), for reasons of record in paper number 11022004.

3. Claims 13, 2, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Bandyopadhyay et al (1994), for reasons of record in paper number 11022004.

4. Claims 13, 2, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Collier et al (US Pat. 5,451,519), for reasons of record in paper number 11022004.

Response to Arguments

5. The rejection of claims 13, 2, 4 and 7 under 35 U.S.C. 102(b) as being anticipated by Torreblanca et al(1996) is traversed on the grounds that :

a. Torreblanca et al does not disclose immunogenic compositions ;

b. Does not disclose a pharmaceutically acceptable excipient;

c. Does not disclose an attenuated form of a live bacteria; and

d. Does not disclose a second heterologous immunoprotective antigen as now recited in claim 13.

6. It is the position of the examiner that :

(response to paragraph a. above) The Salmonella strains of Torreblanca et al are immunogenic compositions; this is an inherently characteristic of a live Salmonella strain of bacteria. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Atlas same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art. US Pat. 5,662,908 provides evidence that mutant strain of Salmonella typhimurium are immunogenic

(see claim 7). No evidence has been submitted to show Salmonella bacteria are not immunogenic.

(response to paragraph b. above) A diluent (a species of the instantly claimed excipients), specifically nutrient broth with added NaCl or E-medium without citrate together with glucose or lactose (see Torreblanca et al, page 16, col. 2, paragraph 2). The instant Specification defines excipient to include diluents . "Preferably, the compositions comprise a pharmaceutically acceptable excipient. A pharmaceutically acceptable excipient is a relatively inert substance that facilitates administration of a pharmacologically effective substance. For example, an excipient can give form or consistency to the vaccine composition, or act as a diluent."

(response to paragraph c. above) With respect to Applicant's assertion that Torreblanca et al does not disclose an attenuated strains of Salmonella, it is the position of the examiner that Torreblanca et al screened for abnormal colony morphology and slow growth, characteristics of attenuated bacteria that have been mutagenized. (see page 18, col. 2, Results section, bottom of column and page 19, col. 1, first two paragraphs "twenty candidates forming abnormal colonies"). Additionally, Torreblanca et al produced strains that lacked and overproduced Dam methylase activity (see page 20, col. 2, paragraphs 3-4). While Torreblanca et al does not use the term "attenuated" in the narrative of the article, the strains of bacteria that are mutated and evidence altered Dam activity , are inherently attenuated and evidenced abnormal cell morphology and colonies.

7. (response to paragraph d. above) has not been amended to recite a second heterologous immunoprotective antigen, but recites the phrase "a first heterologous sequence expresses a heterologous immunoprotective antigen"; Applicant's traversal is not commensurate in scope with the instantly claimed invention.

In response to Applicant's traversal that the authors do not specifically alter dam activity, it is the position of the examiner that Torreblanca et al produced both deletion and insertional mutants of the dam gene. They selected for specific phenotype strains based upon their genotypes from DNA restriction patterns (see page 19, col. 1, paragraph 2, Table 1; Figure

3). The rejection of the claims was under 35 USC 102(b), not 103, over the claimed compositions. Inherently the reference anticipates the instantly claimed invention.\

8. The rejection of claims 13, 2, and 7 under 35 U.S.C. 102(b) as being anticipated by Bandyopadhyay et al (1994) is traversed on the grounds that Bandyopadhyay et al do not state that the E.coli compositions are immunogenic or attenuated and the specification does not define pharmaceutically acceptable excipient to include any diluent.

9. The mutated E.coli stains evidence altered Dam activity, and inherently are attenuated due to the overproduction of Dam activity which resulted in hyper-mutability (see page 69, col. 1-2).

10. With respect to culture medium serving as a vaccine diluent, the Examiner went to US-Pat Full and found culture medium contained in vaccine compositions in US Pat. 4338335 claim 1; US Pat. 6210683 claim 10; US Pat. 6410033 claim 24; USPat. 6136318 claim 23; US Pat. 5961982 claim 3; US Pat. 4985244 claims 1-3; US Pat. 6713073 Detailed Description paragraph 14 to name a few. Therefore culture medium can be included into a vaccine as a diluent for living cells. A culture medium containing living cells is not just any diluent, but one that aids in maintaining cellular viability and is not toxic to the cells. The composition of Bandyopadhyay et al still inherently anticipates the instantly claimed invention as now claimed.

11. The rejection of claims 13, 2, and 7 under 35 U.S.C. 102(b) as being anticipated by Collier et al (US Pat. 5,451,519) is traversed on the grounds that 2YT broth is not a diluent.

12. It is the position of the examiner that the composition of Collier et al (US Pat. 5,451,519) inherently comprises the recited functional characteristics of the instantly claimed invention. No structurally distinguishing components have been set forth in the claims. The cited patent cited immediately above showing culture medium serves as a vaccine diluent is incorporated in response to Applicant traversal hereto.

1. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or

unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

2. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states AArtisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

New Claim Limitations/New Grounds of Rejection

Claim Rejections - 35 USC § 112

3. Claims 13 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

4. Claims 13 and 20 have been amended require the attenuated live bacteria to express an immunoprotective HIV antigen.

5. The specification fails to teach how to formulate and use the claimed immunogenic compositions that express an HIV immunoprotective antigen. The term "immunoprotective antigen" encompasses the ability of the specific antigen to induce protective immunity to HIV infection or disease induction.

6. The specification does not provide substantive evidence that the claimed immunogenic compositions that express an HIV antigen are capable of inducing protective immunity, nor encode and express an immunoprotective antigen (amended claim 13). This demonstration is required for the skilled artisan to be able to make and use the claimed vaccines for their intended purpose of preventing HIV infections and disease. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed immunogenic compositions, i.e. would not be able to accurately predict if protective immunity has been induced.

The ability to reasonably predict the capacity of a single HIV viral antigen immunogen to induce protective immunity is problematic in light of the teachings of Uberla (PLOS Medicine, April 2005, Vol. 2(4), page e119), Excler (Indian J. Med. Res., Vol. 121, April 2005, pages 568-581) and Graham et al (March 1, 2005, Journal of Infectious Diseases, Vol. 191, pages 647-649) who all provide evidence that No HIV vaccine antigens are known in the art, as well as describe compositions that were previously thought to be able to induce an immunoprotective immune response but failed to do so in clinical trails (Graham et al,2005, page 647, col. 1 "The trail was successfully conducted and showed that the vaccine **did not** prevent HIV-1 infection"). The instantly claimed invention that requires the claimed attenuated live bacteria to express an immunoprective antigen against HIV is not enabled.

7. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 4 depends from claims 2 and 13 respectively and defines the second heterologous sequence to be "operatively inserted into a second plasmid", and also recites the newly amended combination of claim limitations set forth in claim 4 which are "wherein the dam gene is non-revertably inactivated by a second heterologous nucleotide sequence". This combination of claim limitations does not evidence original descriptive support in the instant Specification, as the instant Specification does not disclose a genus of living bacteria that carry their native dam gene of a plasmid which is non-revertably inactivated by a second heterologous nucleotide sequence. The combination of claims 2 and 4 defines the mutation that inactivates the dam gene to be an insertion mutation (inserted into a plasmid, claim 4), but a genus of bacteria that carry their dam gene on a plasmid have not been described. Claim 4 recites New Matter in light of the newly submitted combination of claim limitations submitted on Amendment.

8. Claims 13, 2,4 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions that comprise attenuated Salmonella typhimurium Dam- strains that are able to induce a protective immune response against heterologous serotypes (see instant Specification, Table 2, [00265]), and the dam mutant strains of living bacteria that are able to express heterologous antigens to induce an immune response, does not reasonably provide enablement for the instantly amended genus of immunogenic

compositions that comprise a heterologous coding sequence for the expression an immunoprotective antigen that induces an immunoprotective immune response to the heterologous encoded antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

9. The instant Specification teaches that a critical element of the inducing a protective immune response is a minimum immunizing dose of $10^{+}5$ Dam bacteria (see page 81, [00273]; the instantly claimed compositions do not comprise this critical element. Additionally, the instant specification at paragraph [00274], "suggests the *possibility* that Dam- vaccines may have therapeutic application to the treatment of a pre-existing microbial infections." While the instant Specification suggests that the Dam- strains of live bacteria may be therapeutic against the heterologous encoded antigen, this does not disclose, nor provide sufficient guidance to one of skill in the art to enable the utilization of any coding region for any antigen from any strain or species of Vibrio cholera, any respiratory microorganism, any sexually transmitted disease, any immunogenic portion of Hepatitis B surface antigen, any pathogenic virus including HIV virus, any antigen from any pathogenic bacteria or any antigen from any enteric pathogenic microorganism to induce an immunoprotective immune response.

The specification fails to teach how to formulate and use the claimed immunogenic compositions that must function to induce a immunoprotective immune response and thus serve as a vaccine composition. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity against infection and disease induction. The prior art teaches immunogenic compositions that are ineffective as vaccines: hepatitis B antigen that was

ineffective in protecting lamivudine-treated patients against hepatitis viral infection (see title and entire document; Journal of Hepatology, 2004); attenuated rabies virus compositions were ineffective in protecting against infection (Rupprecht et al, 1990, title, abstract only); P55 Borrelia burgdorferi protein was immunogenic but non-protective against disease (Infection and Immunity, Jan 1996). The specification does not provide substantive evidence how any antigen can be turned into an immuoprotective antigen in the claimed immunogenic compositions. This demonstration is required for the skilled artisan to be able to use the claimed composition for their intended purpose of inducing an immunoprotective immune response. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced.

The ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the at protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. See Boslego et al. wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use an immunogenic composition that comprises any antigen to induce an immunoprotective immune response.

The specification fails to teach what characteristics are required for an antigen to the newly claimed immunoprotective immune response. Further, the specification fails to provide an adequate written description of what the coding sequences are of the polynucleotides that encode the immunoprotective antigens claimed as a genus of antigens for the plurality of pathogens in the Markush group of claim 13. A functionally recited characteristic does not structurally define an unpredictable structural antigen that would induce an immunoprotective immune response in any host animal. Therefore, the skilled artisan would be required to de novo locate, identify and characterize the claimed coding sequences for the immunoprotective antigens for the claimed genus of pathogens. This would require undue experimentation given the fact that the specification is completely lacking in teachings, and guidance as to how to make and use an immunoprotective antigen from any antigen obtained from any of the claimed pathogens. The instantly, newly amended, claimed invention is only enabled for a scope of what is now claimed.

Conclusion

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
May 9, 2005

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